Optimizing follow-up after Adult Granulosa Cell Tumor

ANNIINA FÄRKKILÄ, MD PHD
POST DOC, RESIDENT IN OB GYN
UNIV. OF HELSINKI AND HELSINKI UNIVERSITY CENTRAL HOSPITAL
MD, PhD

- Postdoctoral fellow at University of Helsinki

Resident in Ob Gyn, Helsinki University Hospital

No conflicts of interest
Adult-type GCT (AGCT)

- Incidence; 0.5-1.6/100 000
  (Shumer & Cannistra 2003, Unkila-Kallio et al. 1998)
- Diagnosis; age 54 years
- Hormonally active: Produces E2, Inhibins
- Symptoms
  45% Abnormal vag. bleeding (Em pathology in 60%)
  25% Abdominal pain
  14% Abdominal distention
  14% No symptoms
- Signs; Unilateral ovarian solid mass
  - Thick endometrium
  - 90% Stage I
AGCT — pathogenesis

Somatic point mutation in transcription factor FOXL2 (402C->G)  
(Shah et al, 2009)

- Present in 90-97% of AGCTs  
(Shah et al 2009, Jamieson 2010)

- Normal FOXL2; gonadal differentiation; Granulosa cells -> Sertoli-like cells  
(Uhlenhaut et al 2009)

- FOXL2 402C->G mutation;
  - Post-translational modifications  
(Kim et al 2014)
  - Impaired interaction with co-factors
  - Differential expression of genes regulating TGFß pathway and hormone production  
(Rosario et al 2014)
  - Increased proliferation and decreased apoptosis  
(Kim et al 2010)
Follow-up after AGCT

1. Rationale of follow-up?

2. Identifying an increased risk of relapse
   - Correct diagnosis!
   - Prognostic factors
     - Clinical
     - Molecular

3. Performing Clinical follow-up
   - Follow-up patterns
   - Blood samples
Why follow-up?

Aiming for
1. Improved overall survival
2. No increased morbidity
3. Quality of life

In epithelial ovarian cancers (EOC)
- Serum marker surveillance has not improved survival in epithelial ovarian cancers (EOC)
- Early chemotherapy based on follow-up increased morbidity and decreased quality of life (Rusdin et al, 2010)

BUT; AGCT is not EOC!
- AGCT surgical treatment is often feasible in the relapse; 71-85% optimal surgery at relapse (Ertas et al, 2014)
- Increased chances of complete removal of the local recurrent tumor if detected early (Fleming et al, 2011)
- Complete removal of relapse associated with increased survival in AGCT (Mangilil et al, 2013)
Who to follow-up?

1. Most early stage — 25% risk of relapse

2. Higher risk in some patients
   - Identification/prognostic factors
   - Careful follow-up of the high-risk patients
   - Avoiding unnecessary examinations and worry in low-risk disease

<table>
<thead>
<tr>
<th>Stage (FIGO 2009)</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>218</td>
<td>(85.2%)</td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>(4.3%)</td>
</tr>
<tr>
<td>Ia</td>
<td>130</td>
<td>(50.8%)</td>
</tr>
<tr>
<td>Ib</td>
<td>4</td>
<td>(1.6%)</td>
</tr>
<tr>
<td>Ic</td>
<td>73</td>
<td>(28.5%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>23</td>
<td>(9.0%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>10</td>
<td>(3.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Stage 1a</th>
<th>Stage 1c</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>13.0%</td>
<td>36.7%</td>
<td>20.5%</td>
</tr>
<tr>
<td>50-</td>
<td>36.4%</td>
<td>52.4%</td>
<td>42.1%</td>
</tr>
</tbody>
</table>
Correct diagnosis

- AGCT presents with a wide range of different histologies
  - AGCT is rare; diagnosis can be difficult for even experienced pathologist
  - 20-40% false diagnosis in historical series (Cronje et al 1999, Bryk et al 2015)
- FOXL2 402 C->G mutation is specific to AGCTs
  - Easily feasible assay
    - DNA from diagnostic samples (FFPE)
    - qPCR-based TagMan Allelic Discrimination
  - Validated for clinical use in difficult cases (Kommoss et al, 2013)
Effect of molecular diagnosis on outcomes?

- Three cohorts;
  - n=248 Helsinki, Finland
  - n=79 Amsterdam, the Netherlands
  - n=42 Tübingen, Germany
Misdiagnosed tumors

Table 2: Histology of FOXL2 wt tumors after final review

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian carcinoma</td>
<td>17</td>
<td>(29)</td>
</tr>
<tr>
<td>mAGCT FOXL2 wild-type</td>
<td>12</td>
<td>(21)</td>
</tr>
<tr>
<td>Seroid cell tumor</td>
<td>4</td>
<td>(7 )</td>
</tr>
<tr>
<td>Thecoma</td>
<td>4</td>
<td>(7 )</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>3</td>
<td>(5 )</td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumor</td>
<td>3</td>
<td>(5 )</td>
</tr>
<tr>
<td>Sex cord stromal tumor with annular tubules</td>
<td>3</td>
<td>(5 )</td>
</tr>
<tr>
<td>Fibroma</td>
<td>2</td>
<td>(4 )</td>
</tr>
<tr>
<td>Brenner tumor</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Cellular Fibroma</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Juvenile GCT</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>FATWO*</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Sex cord stromal tumor</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Transi cellular carcinoma</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>ND</td>
<td>3</td>
<td>(5 )</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

* Female Adnexal Tumor of probable Wolffian Origin

(Mc Conechy et al JNCI, In press)
Outcomes

AGCT
AGCT – FOXL2 wt
Misdiagnosed tumors

(Mc Conechy et al JNCI, In press)
## Survival

<table>
<thead>
<tr>
<th>Follow-up Time</th>
<th>Reverse KM</th>
<th>OS % (95%CI)</th>
<th>Deaths</th>
<th>DSS % (95%CI)</th>
<th>Deaths of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse KM</td>
<td>10.49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS % (95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year</td>
<td>93.3 (91.5-98.4)</td>
<td>92 (35.9%)</td>
<td>97.4 (95.3-99.5)</td>
<td>42 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>10-year</td>
<td>84.4 (79.5-89.5)</td>
<td>164 (64.1%)</td>
<td>91.8 (88.0-95.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-year</td>
<td>72.1 (65.6-79.2)</td>
<td></td>
<td>85.4 (80.0-91.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Deaths
- Yes: 92 (35.9%)
- No: 164 (64.1%)

### Disease Specific Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year</th>
<th>10-year</th>
<th>15-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>100</td>
<td>97.1</td>
<td>95.1</td>
</tr>
<tr>
<td>Ic</td>
<td>97.8</td>
<td>92.8</td>
<td>86.4</td>
</tr>
<tr>
<td>II-III</td>
<td>100</td>
<td>74.1</td>
<td>63.5</td>
</tr>
</tbody>
</table>

(Mc Conechy et al JNCI, In press)
AGCT survival compared to general population

- 165 Verified AGCT patients from Helsinki, Finland (Blue crosses)
- Life expectancies of age, gender and year – matched general population from Finland (Red line)

(Mc Conechy et al JNCI, In press)
**AGCT relapses**

### Number of Patients with Recurrent Disease

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90</td>
<td>143</td>
<td>23</td>
</tr>
<tr>
<td>%</td>
<td>35.2%</td>
<td>55.9%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

### % Relapsed by Age and Stage

<table>
<thead>
<tr>
<th>Age Grp</th>
<th>Stage Ia</th>
<th>Stage Ic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Recurrence</td>
<td>Recurred</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>27 (58.7%)</td>
<td>19 (41.3%)</td>
</tr>
<tr>
<td>51-65</td>
<td>44 (88.0%)</td>
<td>6 (12.0%)</td>
</tr>
<tr>
<td>65</td>
<td>9 (75.0%)</td>
<td>3 (25.0%)</td>
</tr>
</tbody>
</table>

### % NOT Relapsed by Stage

<table>
<thead>
<tr>
<th>RFS</th>
<th>Stage</th>
<th>5-year</th>
<th>10-year</th>
<th>15 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>93.7</td>
<td>80.2</td>
<td>76.2</td>
<td></td>
</tr>
<tr>
<td>Ic</td>
<td>84.8</td>
<td>63.6</td>
<td>40.7</td>
<td></td>
</tr>
<tr>
<td>II-III</td>
<td>88.9</td>
<td>53.3</td>
<td>53.3</td>
<td></td>
</tr>
</tbody>
</table>

**High-risk; Stage Ic <50 years**

**Low-risk; >50 years AND stage Ia**
Time to relapse

Median time to relapse; 7.2 years
Range; 1 - 27 years

Relapses 33% within 5 years
78% within 10 years
95% within 15 years

(Mc Coneghy et al, 2016,
Farkkila et al, 2014)
Prognostic factors

A Disease-free survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Stage I  HR (95% CI) p-value</th>
<th>Stage Ia  HR (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GATA4</td>
<td>4.99 (1.14-34.21), 0.0322</td>
<td>7.71 (1.12-151.85), 0.0375</td>
</tr>
</tbody>
</table>

(Färkkilä et al, 2014)

B Disease specific survival
When and How to follow-up?

International guidelines:
- USA; National Comprehensive Cancer Network (NCCN)
- Europe; European Society of Medical Oncology (ESMO)

- **Follow-up scheme**
  - First 2 years; every 2-4 months
  - 2-5 years; every 6 months
  - > 5 years; yearly, until progression

- **Examinations**
  - History
  - Physical & pelvic exam
  - Tumor markers; Inhibin suggested
  - Ultrasound if the other ovary has not been removed (every 6 months)
  - CT scan only when necessary
Follow-up marker

Inhibin B is the current marker

- Significantly superior to Inhibin (total) or Inhibin A (*Mom 2007*)
- Fluctuates during menstrual cycle
- 10-15% AGCTs are Inhibin B negative

Anti-Müllerian Hormone (AMH)

- AMH and Inhibin B positively correlate to tumor size
- AMH and Inhibin B are equal in detecting AGCT

(Färkkilä et al, 2015)
AMH and Inhibin B are highly sensitive and specific

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMH</td>
<td>92%</td>
<td>82%</td>
</tr>
<tr>
<td>Inhibin B</td>
<td>93%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Combination of AMH and Inhibin B is superior to inhibin B alone

All samples (n=514)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AMH</td>
<td>0.92 (0.88-0.95)</td>
</tr>
<tr>
<td>InhB</td>
<td>0.94 (0.90-0.96)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.95 (0.91 -0.97) *0.03 (InhB)</td>
</tr>
</tbody>
</table>

Lead times; 3,4 years for AMH
2.8 years for Inhibin B

(Färkkilä et al, 2015)
Optimal follow-up?

1. Correct diagnosis
   ◦ FOXL2 mutation assay should be performed to all AGCT suspicions

2. Identification of high-risk patients
   ◦ Stage Ic, or tumor rupture
   ◦ < 50 years

3. Follow-up Scheme
   ◦ Only 1/3 of the relapses come within the first 5 years
   ◦ Median time to relapse 7-8 years
   ◦ Yearly follow-ups for up to 15 (20) years? At least in high risk patients.
   ◦ Mammography! – increased risk of breast cancer; 1-20% (Ohel 1983), 3.3x (Hammer 2013)
   ◦ Endometrial assessment (ultrasound/biopsy) if uterus was not removed

4. AMH and Inhibin B are sensitive and specific serum markers
   ◦ Evaluation of both markers at diagnosis
   ◦ Combination or Inhibini B alone to be utilized during follow-up

5. New studies are needed to evaluate the effect of follow-up on survival, morbidity and quality of life!
Thank you!

The Heikinheimo Lab
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Marjut Pihlajoki, Noora Andersson
Leila Unkila-Kallio
Mikko Anttonen etc.

www.gctgrouphelsinki.com

Collaborators;
Univ of Oulu& Turku, Finland
Melissa McConeghy, Blake Gilks,
David Huntsman et al. Univ. of British Columbia, Vancouver, CA
Hugo Horlings, Amsterdam University Hospital, The Netherlands
Powel Crosley, Edmonton, CA
David B. Wilson, St Louis, USA

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TRAIL is a promising target for therapy in AGCTs

Circulating levels of TNF-related apoptosis inducing-ligand are decreased in patients with large adult-type granulosa cell tumors—implications for therapeutic potential

Anniina Färkkilä, Giorgio Zauli, Ulla-Maija Haltia, Marjut Pihlajoki, Leila Unkila-Kallio, Paola Secchiero & Markku Heikinheimo

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